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Review

Impact of the introduction of the pneumococcal conjugate vaccine in the Brazilian routine childhood national immunization program☆

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ABSTRACT

Brazil introduced the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, *Synflorix*™, GSK Vaccines) in the routine childhood immunization program in 2010 with a 3 + 1 schedule (with catch-up for children <2 years-old). This review represents the first analysis of the overall impact of a second-generation pneumococcal conjugate vaccine on nasopharyngeal carriage and all the major pneumococcal disease manifestations in a single, pneumococcal conjugate vaccine-naïve, developing country. A total of 15 published articles and 13 congress abstracts were included in the analysis. In children <5 years-old, studies showed a positive impact of PHiD-CV on the incidence of vaccine-type and any-type invasive pneumococcal disease (including decreases in pneumococcal meningitis morbidity and mortality), on pneumonia incidence and mortality, and on otitis media. Nasopharyngeal carriage of vaccine-type and any-type pneumococci decreased after the primary doses, with no early signs of replacement with other pathogens. Finally, herd protection against vaccine-type invasive pneumococcal disease and pneumonia in unvaccinated subjects was shown in some studies for some age groups. In conclusion, pneumococcal disease decreased after the introduction of PHiD-CV into the Brazilian national immunization program. Further follow-up is needed to evaluate the long-term overall impact of PHiD-CV in the Brazilian population.

1. Introduction

The diseases caused by *Streptococcus pneumoniae* are a leading cause of morbidity and mortality in children <5 years-old worldwide, especially in developing countries [1–4]. Pneumococcal diseases range from life-threatening invasive pneumococcal diseases (IPD) such as meningitis, bacteremia, and bacteremic pneumonia, to the less serious but more frequent non-invasive pneumonia and acute otitis media (AOM) [1].

Brazil is a large, upper middle-income country composed of five regions with different climatic, demographic, and socioeconomic characteristics. It has a mixed ethnic population of approximately 200 million with approximately 3 million births per year [5,6]. Brazil was the first country in Latin America to introduce the 10-valent pneumococcal non-typeable *Haemophilus influenzae* (NTHi) protein D conjugate vaccine (PHiD-CV; *Synflorix*™, GSK Vaccines) into its routine national immunization program for all children [7].

PHiD-CV contains ten capsular polysaccharides from serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, eight of them being conjugated to the cell-surface protein D from NTHi, serotype 18C conjugated to tetanus toxoid, and serotype 19F conjugated to diphtheria toxoid. Implemented between March and September 2010, the recommended vaccination schedule includes three primary doses at 2, 4, and 6 months of age followed by a booster dose at 12–15 months of age (3 + 1 schedule) [7]. Catch-up schedules were also set up by the Ministry of Health for older children: two primary doses and a booster at 12–15 months were recommended for infants 7–11 months-old, and one dose for children 12–23 months-old. For high-risk children, the vaccine was recommended up to 5 years of age. In 2016, reduction to a 2 + 1 schedule (2 and 4 months of age, and booster at 12 months of age) was put in place [8].

Abbreviations: AOM, acute otitis media; CI, confidence interval; CVE, Centro de Vigilância Epidemiológica; IAL, Instituto Adolfo Lutz; IPD, invasive pneumococcal disease; NS, statistically non-significant; NTHi, non-typeable *Haemophilus influenzae*; NVT, non-vaccine type; PCV, pneumococcal conjugate vaccine; PHiD-CV, pneumococcal *Haemophilus influenzae* protein D conjugate vaccine; PM, pneumococcal meningitis; RCTs, randomized controlled trials; SINAN, Notifiable Diseases Information System; VE, vaccine effectiveness; VT, vaccine-type.

☆ *Trademarks*: Synflorix is a trademark of the GSK group of companies. Prevenar/Prevnar is a trademark of Pfizer/Wyeth LLC.

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Brazil has a national surveillance system of meningitis through the Notifiable Diseases Information System (SINAN for *Sistema de Informação de Agravos de Notificação*) and the national reference laboratory for meningitis and pneumococcal infections (IAL for *Instituto Adolfo Lutz*, São Paulo). The municipalities or states also have the possibility to register morbidity and mortality data for other non-mandatory pneumococcal diseases via the unified health system. Thus, 5 years after the introduction of PHiD-CV, Brazil offers an opportunity to measure the impact of the vaccine on pneumococcal disease in a large pediatric population in a country with high vaccine coverage and available surveillance systems [9,10].

In this review, we examined the impact of PHiD-CV introduction in the Brazilian national immunization program on IPD, pneumonia, AOM, and nasopharyngeal carriage. We also examined herd protection in unvaccinated age groups.

2. Methods

2.1. Search strategy and selection criteria

We conducted a search of the literature in three different online databases (PubMed, Embase, and SciELO) to identify reports of studies investigating the possible effects of PHiD-CV

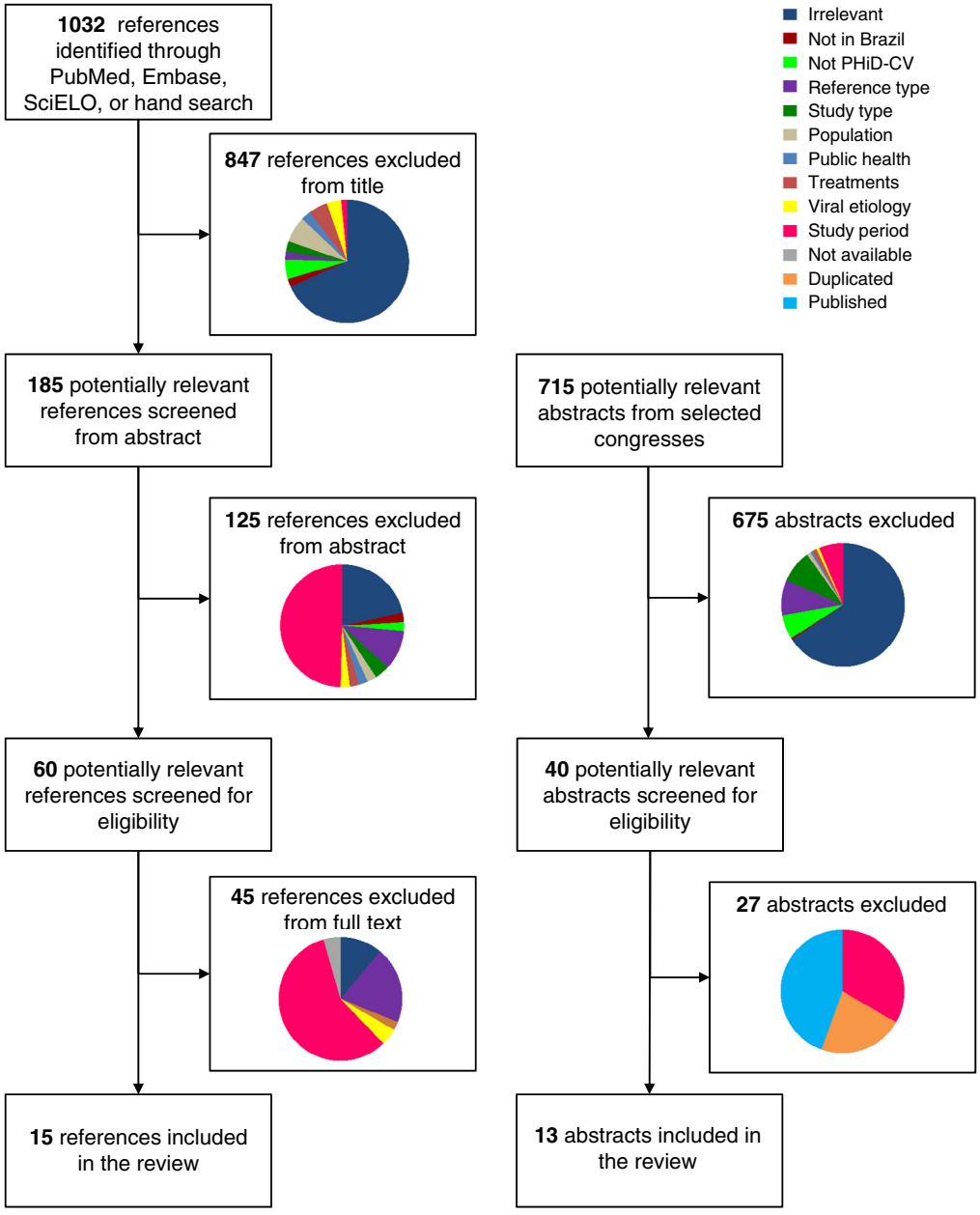


Fig. 1. Flow chart of the articles and congress abstracts evaluated for inclusion in the review. Reasons for exclusions were: irrelevance (studies not analyzing *Streptococcus pneumoniae*, pneumococcal diseases, or topic-related diseases), not in Brazil (studies performed in other countries), not PHiD-CV (studies of vaccines other than PHiD-CV), reference type (case reports, reviews, editorials, or comments), study type (animal studies, in vitro studies, models, or vaccine immunogenicity or safety studies), population (studies conducted among populations with chronic diseases not representative of the general population or, for topic-related diseases, in too-old populations), public health (public health programs or recommendations, cost-effectiveness or health economics studies), treatments (studies evaluating treatments such as antibiotics), viral etiology (studies of virus etiology only), study period (studies conducted only before or after PHiD-CV introduction or whose analysis period was unspecified), not available (full text not available), duplicated (studies presented several times), and published (congress abstracts whose results were also described in a published article included in the analysis).

on pneumococcal disease in Brazil [11–13]. Reports had to be in English, Portuguese, or Spanish and published between January 2011 and April 2015. Search terms included various combinations of terms as described in Supplementary Appendix A. Additional searches were done in PubMed to identify articles published between April and November 2015, and between December 2015 and February 2016.

We included all randomized controlled trials (RCTs), non-randomized studies, and observational studies assessing the effects of PHiD-CV introduction in Brazil on IPD, pneumonia, AOM, nasopharyngeal carriage, or herd protection in all age groups. The year of PHiD-CV introduction, 2010, was considered as a transition period. We also included studies evaluating vaccination coverage rate after PHiD-CV introduction. In addition, we included articles that evaluated the prevalence or incidence of other diseases related to the same topics (bronchitis, bronchiolitis, asthma, reactive airway disease, sinusitis, pharyngitis, tonsillitis, and conjunctivitis) before and after 2010 in children ≤5 years-old.

We excluded reports of animal or in vitro studies; immunogenicity or safety studies; cost-effectiveness studies; public health recommendations; case reports; editorials; studies of viral etiology only; studies conducted among populations with chronic diseases not representative of the general population; or studies whose analysis period was unspecified. Reviews were excluded but their bibliographies were examined for additional potentially relevant articles.

First, two reviewers independently screened the titles of all retrieved articles. Then, three different reviewers independently screened the abstracts of the selected articles for relevance. In a third step, the full texts of the selected reports were assessed for eligibility using pre-defined inclusion and exclusion criteria. At all stages, reviewers reached a consensus for inclusion or exclusion of the articles.

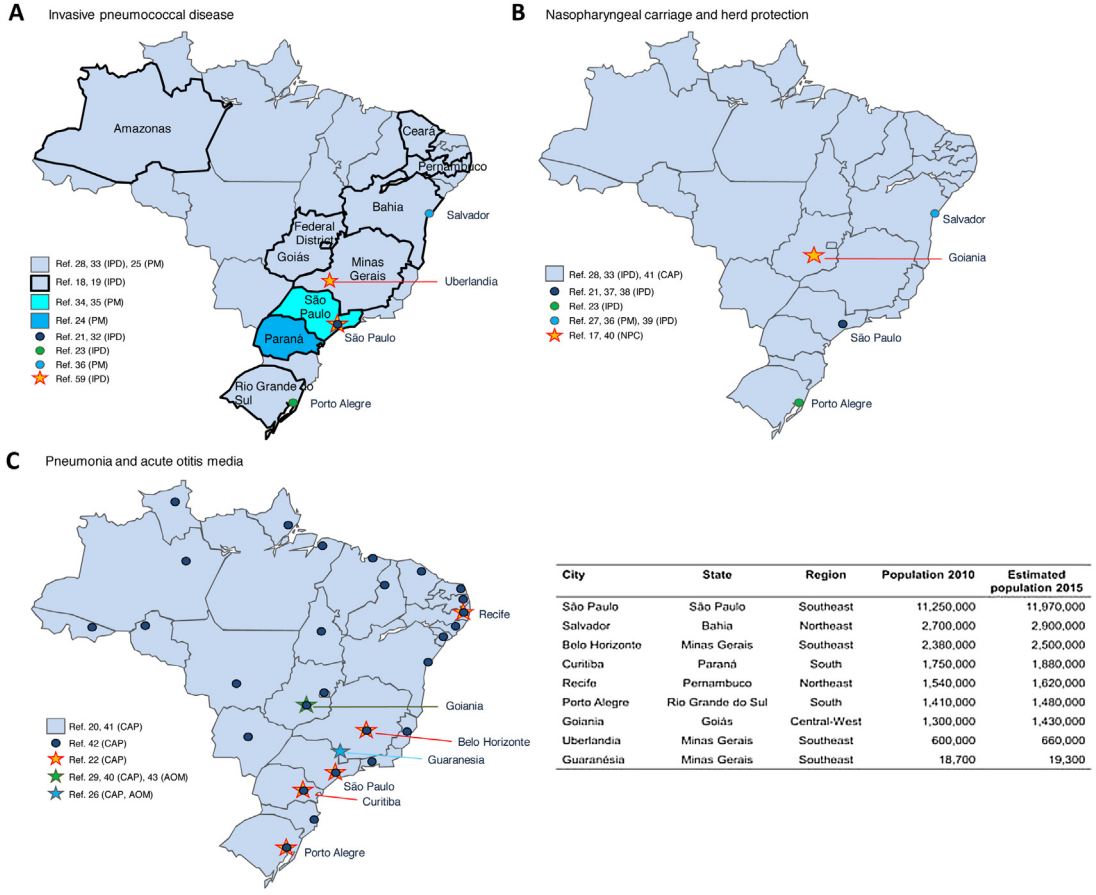
We also searched the abstracts of relevant scientific congresses held between January 2011 and May 2015 (Supplementary Appendix A) and screened them with the same inclusion and exclusion criteria used for the articles. Abstracts were not included if the results were also described in a published article included in the analysis. When several abstracts were presented for the same study, the most recent or most complete data were used.

Finally, we searched for additional epidemiological data on the websites of SINAN, Centro de Vigilância Epidemiológica (CVE) "Alexandre Vranjac" in São Paulo, and the Brazilian government open-access public health database system DATASUS [14–16].

3. Results

3.1. Results of the literature search

The literature search identified 1032 potentially relevant articles, of which 60 were retrieved for full text analysis (Fig. 1). Of them, 15 met the inclusion criteria and were included in the analysis. Two studies were case–control studies [17,18], one was an indirect cohort study [19], and ten were time-series or cross-sectional analyses [20–29]. Two articles described only coverage



City	State	Region	Population 2010	Estimated population 2015
São Paulo	São Paulo	Southeast	11,250,000	11,970,000
Salvador	Bahia	Northeast	2,700,000	2,900,000
Belo Horizonte	Minas Gerais	Southeast	2,380,000	2,500,000
Curitiba	Paraná	South	1,750,000	1,880,000
Recife	Pernambuco	Northeast	1,540,000	1,620,000
Porto Alegre	Rio Grande do Sul	South	1,410,000	1,480,000
Goiania	Goiás	Central-West	1,300,000	1,430,000
Uberlandia	Minas Gerais	Southeast	600,000	660,000
Guaranésia	Minas Gerais	Southeast	18,700	19,300

Fig. 2. Brazilian regions and cities with data included in this analysis. (A) Invasive pneumococcal disease in children <5 years-old. (B) Nasopharyngeal carriage in children <5 years-old and herd protection in unvaccinated age groups. (C) Pneumonia and acute otitis media in children <5 years-old. Population data was based on 2010 census (http://cidades.ibge.gov.br/xtras/home.php) and maps were obtained from the Presentation Magazine website (http://www.presentationmagazine.com/editable-maps). AOM, acute otitis media; CAP, community-acquired pneumonia; IPD, invasive pneumococcal disease; NPC, nasopharyngeal carriage; PM, pneumococcal meningitis.

rates [9,30]. In addition, 13 out of the 715 screened congress abstracts were included.

3.2. Vaccination coverage

The Brazilian Ministry of Health provides information on vaccination coverage based on the number of administered doses registered in an administrative database (DATASUS). At the national level, the coverage for the three primary doses of PHiD-CV was 24% in 2010, 82% in 2011, 88% in 2012, 94% in 2013, and 93% in 2014 [31]. Preliminary data for 2015 suggested that coverage for the three primary doses was similarly high. These data were referred to in several studies [20,28,30,32,33]. However, coverage rates differed by city. Soon after the introduction of PHiD-CV, coverage rates for the three primary doses in Belo Horizonte, Curitiba, and Recife reached approximately 100%, whereas coverage was 85% in Porto Alegre and 75% in São Paulo in July 2011 [22]. In Goiania, two studies showed similar lower coverage rates [9,29]. A household survey performed from December 2010 to February 2011 indicated coverage of 53.4% for the three primary doses [9]. An active population-based surveillance study indicated that the overall coverage rate for a complete 3-dose primary series before 12 months of age was 58%, with a lower rate for 24–35 months-old (50.3%) than for 2–23 months-old (61%) [29]. No information was published about coverage for the booster dose administered in the second year of life.

3.3. Invasive pneumococcal disease

3.3.1. In the vaccinated cohort

Seven articles and six abstracts analyzed the effect of PHiD-CV on IPD or pneumococcal meningitis only in young children (Fig. 2A, Table 1). A matched case–control study published in 2014 was conducted in ten Brazilian states using laboratory- and hospital-based surveillance to identify IPD cases among children eligible to have received at least one dose of PHiD-CV [18]. The analysis included 316 IPD cases and 1219 age- and neighborhood-matched controls from March 2010 through December 2012. The adjusted vaccine effectiveness (VE) against vaccine-type (VT) IPD was 83.8% (95% confidence interval [CI], 65.9–92.3%) for an age-appropriate vaccine schedule and 68.0% (95% CI, 17.6–87.6%) for one catch-up dose in children aged 12–23 months. In addition, VE against IPD was 87.7% (95% CI, 60.8–96.1%) for serotype 14 and 82.8% (95% CI, 23.8–96.1%) for serotype 6B (the two most common vaccine serotypes) and 82.2% (95% CI, 10.7–96.4%) for the vaccine-related serotype 19A [18]. Using these 316 cases, the same group performed an indirect cohort analysis, in which the vaccination status of patients with VT IPD was compared with that of non-vaccine-type (NVT) IPD [19]. The results of this analysis were consistent with those of the case–control study, with adjusted effectiveness of ≥1 dose of 72.8% (95% CI, 44.1–86.7%) against VT IPD and of 61.3% (95% CI, 14.5–82.5%) against vaccine-related IPD.

Several observational studies have shown a decrease in IPD incidence after PHiD-CV introduction in Brazil. A time-series analysis conducted in a university hospital in São Paulo between 2006 and 2012 showed an 80% decrease in the overall IPD incidence rate per 1000 admissions among <2 years-old (from 20.3 to 3.97) and a 97% decrease in VT IPD incidence rate (from 16.47 to 0.44) after PHiD-CV introduction [21]. A laboratory-based national surveillance in reference hospitals showed that, 2 years after PHID-CV introduction, VT IPD cases numbers decreased by 85% in vaccinated children [33]. In a sentinel hospital in São Paulo for 2009–2012, the annual number of overall IPD and VT IPD cases in <2 years-old decreased by 77% and 89%, respectively, in the post-introduction period [32]. No increase in NVT IPD cases was observed. A reduction in penicillin resistance rates was also observed in this study. Finally, an interrupted time-series analysis using confirmed pneumococcal meningitis cases notified to SINAN and all IPD cases from the national reference laboratory (adjusted for seasonality and secular trends) suggested that PHiD-CV reduced IPD rates by 44.2% (95% CI, 15.8–72.5%) between 2008–2009 and 2011–2013 [28]. In contrast to all other studies on IPD, in Porto Alegre, a study analyzing 325 pneumococcal strains isolated from IPD patients of all ages between 2007 and 2012 showed that, in ≤2 years-old, the frequency of VT isolates before and after introduction did not differ (58.8% vs 58.3%; $n = 29$ isolates) [23].

Three studies (reported as two articles and two abstracts) analyzed cases of pneumococcal meningitis reported to SINAN and produced similar results [24,25,34,35]. A cross-sectional retrospective study comparing the incidence and mortality of pneumococcal meningitis in 1998–2009 vs 2010–2011 in Paraná state showed significant reductions in incidence rate/100,000 population (60%, from 6.21 to 2.49) and mortality rate (76%, from 1.92 to 0.47) in <2 years-old [24]. An ecological study that reviewed national data showed a 50% reduction in the incidence rate and 69% in the mortality rate from pneumococcal meningitis in ≤2 years-old between 2007 and 2012 [25]. Preliminary SINAN data also showed that pneumococcal meningitis rates per 100,000 persons in <2 years-old decreased by 50% from an average of 10.2 in the pre-vaccination baseline period (2001–2009) to 5.1 in 2011 [34]. A decrease of 44% was seen when using years 2007–2009 as the baseline [35].

In addition, in a hospital-based surveillance in the city of Salvador, the incidence of pneumococcal meningitis tended to decrease in <2 years-old between January 2008–May 2010 and June 2010–December 2012 ($p < 0.058$) [36]. The overall case-fatality rate decreased from 24% to 17.6%.

3.3.2. In the unvaccinated cohort

To evaluate the herd protection induced by PHiD-CV, its impact on VT IPD has also been assessed in unvaccinated children >2 years-old and adults. Initial results from a retrospective surveillance of IPD in a sentinel hospital in São Paulo showed that, in <16 years-old, the prevalence of VTs decreased after vaccination (62% vs 35.5%) and the prevalence of NVTs did not increase [37]. Changes in overall disease rate, which is a combination of VT and NVT changes, were also assessed. Overall IPD cases/1000 admissions decreased from 4.7 in 2007–2009 to 3.7 in 2010 (transition period) and to 2.2 in 2011–2014 [37,38]. The distribution of clinical diagnoses and IPD mortality did not change over time in this study [38]. Using national surveillance data, a significant herd effect for VT IPD was observed two years after PHiD-CV introduction in all age-groups except in adults ≥65 years-old [33]. Finally, in a prospective laboratory surveillance, the incidence of overall IPD cases/100,000 inhabitants in Salvador declined by 20% in ≥50 years-old (from 0.36 to 0.29), and by 23% in ≥60 years-old (from 0.26 to 0.20) between 2008–2009 and 2010–2013 [39].

Two retrospective hospital-based studies were not able to detect a significant effect on the overall IPD incidence in unvaccinated populations two years after PHiD-CV introduction (Fig. 2B, Table 2) [21,23]. First, in a time-series analysis conducted in a university hospital in São Paulo between 2006 and 2012, no significant effect of PHiD-CV introduction was seen on overall IPD or VT IPD incidence in >15 years-old but the incidence of overall IPD and VT IPD tended to decrease (25% and 65%, respectively) in 2–14 years-old [21]. Second, in the study analyzing 325 strains isolated from IPD patients of all ages in Porto Alegre, no significant difference was seen between the proportion of VT strains isolated before (51.5% in 2007–2010) and after PHiD-CV introduction (48.1% in 2011–2012) [23]. Also, no net effect was observed in unvaccinated 2–17 years-old and an increase was observed in adults ≥18 years in an interrupted time-series analysis using all IPD cases from the national reference laboratory and confirmed pneumococcal meningitis cases notified

Table 1
Impact of PHiD-CV on invasive pneumococcal disease in Brazil in children <5years of age.

Reference	Region/city	Study type	Study period	Sample size	Age group	Outcome	Effectiveness or percent decrease (95% CI)	Incidence or percentage of cases	
								Pre-introduction	Post-introduction
Domingues et al. [18]	10 states	Matched case–control study	March 2010–December 2012	316 cases + 1219 controls (4 age- and neighborhood-matched per case)	<5 years	VT IPD ST6B IPD ST14 IPD Vaccine-related IPD ST19A IPD NVT IPD	83.8% (65.9–92.3%)[a] 81.9% (64.4–90.8%)[b] 82.8% (23.8–96.1%)[a] 87.7% (60.8–96.1%)[a] 77.9% (41.0–91.7%)[a] 82.2% (10.7–96.4%)[a] 37.5% (−65.4 to 76.4%)[a]	–	–
Verani et al. [19]	10 states	Indirect cohort study (Broome method)	March 2010–December 2012	316 cases	<5 years	VT IPD ST6B IPD ST14 IPD Vaccine-related IPD ST19A IPD	72.8% (44.1–86.7%)[b] 73.9% (41.9–88.3%)[a] 69.7% (16.5–89.0%)[b] 65.0% (−8.5 to 88.7%)[a] 75.4% (43.2–89.4%)[b] 75.8% (37.4–90.7%)[a] 61.3% (14.5 to −82.5%)[b] 64.8% (15.3–85.4%)[a] 71.3% (16.6 to −90.1%)[b] 63.4% (−16.8 to 88.6%)[a]	–	–
dos Santos et al. [21]	City of São Paulo	Time-series analysis (University hospital)	Pre: January 2006–June 2010 Post: July 2010–September 2012	259 patients (89 in <2 years)	<2 years	Overall IPD VT IPD NVT IPD	80.4%[c]; $p = 0.0012$ 97.3%[c]; $p = 0.0002$ 18.2%[c]; NS	$20.30/10^3$ $16.47/10^3$ $3.80/10^3$	$3.97/10^3$ $0.44/10^3$ $3.11/10^3$
Caierão et al. [23]	City of Porto Alegre	Retrospective study	Pre: 2007–2010 Post: 2011–2012	325 samples (29 in <2 years)	<2 years <5 years	VT IPD	No decrease[c] No decrease[c]	58.8% 52.4%	58.3% 58%
Berezin et al. [59] (abstract)	Cities of São Paulo and Uberlandia	Retrospective study (2 university hospitals)	Pre: 2005–2009 Post: 2010	135 patients	<5 years	VT IPD	–	71.3%	65.0%
Andrade et al. [28]	Nationwide	Interrupted time-series analysis (IPD data from SINAN and PM cases from IAL)	Pre: 2008–2009 Post: 2011–2013	9827 cases overall	<2 years	Overall IPD	2–23 months: 44.2% (15.8–72.5%)[c]; $p < 0.0001$ 2–11 months: 34.7% (10.4–58.9)[c]; $p = 0.002$ 12–23 months: 61.1% (39.6–82.7)[c]; $p < 0.0001$	–	–
Brandileone et al. [33] (abstract)	Nationwide	Passive surveillance	Pre: 2008–2009 Post: 2011–2012	2399 isolates (174 in <2 years)	<2 years	VT IPD (annual median of isolate numbers)	85%[c]; $p < 0.005$	–	–
Safadi et al. [32] (abstract)	City of São Paulo	Hospital-based surveillance	2004–2012	94 cases	<2 years	VT IPD Overall IPD NVT IPD	89%[c] 77%[c] No increase[c]	–	–
Hirose et al. [24]	State of Parana	Observational, cross-sectional study with retrospective data collection (SINAN)	Pre: 1998–2009 Post: 2010–2011	1339 cases overall	<2 years	PM PM mortality	59.9%[c]; $p < 0.01$ 75.5%[c]; $p < 0.01$	$6.21/10^5$ $1.92/10^5$	$2.49/10^5$ $0.47/10^5$
Grando et al. [25]	Nationwide	Descriptive study and ecological analysis of cases reported to SINAN	Pre: 2007–2009 Post: 2011–2012	1311 cases	≤2 years	PM PM mortality	50.3%[c] 69.2%[c]	$3.70/10^5$ $1.30/10^5$	$1.84/10^5$ $0.40/10^5$

Table 1 (*Continued*)

Reference	Region/city	Study type	Study period	Sample size	Age group	Outcome	Effectiveness or percent decrease (95% CI)	Incidence or percentage of cases	
								Pre-introduction	Post-introduction
Liphaus et al. [34] (abstract)	State of São Paulo	Population-based data from SINAN	Pre: 2001–2009 Post: 2011	1332 cases	<2 years	PM	50%[c]; $p < 0.001$	$10.2/10^5$	$5.1/10^5$
Safadi et al. [35] (abstract)			Pre: 2007–2009 Post: 2011	–	<2 years	PM	44%[c]	$9.2/10^5$	$5.1/10^5$
Lobo et al. [36] (abstract)	City of Salvador	Hospital-based surveillance	Pre: January 2008–May 2010 Post: June 2010–December 2012	104 cases overall	<2 years	PM	Significant decline[c]; $p < 0.058$	–	–

CI, confidence interval; IAL, Instituto Adolfo Lutz; IPD, invasive pneumococcal disease; NVT, non-vaccine type; PM, pneumococcal meningitis; SINAN, Notifiable Diseases Information System; ST, serotype; VT, vaccine-type (serotypes 1, 4, 5, 6B, 7F, 9V, 18C, 19F, and 23F).

[a] Effectiveness of an up-to-date schedule.

[b] Effectiveness of ≥1 dose.

[c] Percent decrease.

to SINAN (adjusted for seasonality and secular trends) between 2008–2009 and 2011–2013 [28].

Preliminary results from a hospital-based surveillance study in the city of Salvador suggested that the incidence of pneumococcal meningitis per 100,000 persons decreased from 0.71 (January 2008–May 2010) to 0.46 (June 2010–December 2012) in all-age patients [36]. Similarly, the incidence of VT pneumococcal meningitis decreased from 0.31 to 0.15 cases/100,000 persons [36]. Another hospital-based surveillance in Salvador also showed that the annual incidence of pneumococcal meningitis cases/100,000 population decreased from 1.65 in 1996 to 0.2 in 2012, and the incidence rate of penicillin nonsusceptible pneumococci decreased 82% over this 17-year period, suggesting an important effect in unvaccinated groups although this study did not compare incidence in <2 and ≥2 years-old [27].

3.4. Pneumonia

3.4.1. In the vaccinated cohort

Eight reports, including four abstracts, evaluated the impact of PHiD-CV introduction on pneumonia (Fig. 2C, Table 3). A retrospective analysis of the governmental open-access public health DATASUS database reported that hospitalization rates for pneumonia in <4 years-old (i.e., including vaccinated and unvaccinated children) decreased by 12.7% between the pre-PHiD-CV period (2002–2009) and the 2 years following PHiD-CV introduction [20]. Notably, the decreasing incidence of pneumonia admissions was not associated with changes in incidence of non-respiratory admissions ($p = 0.39$) [20].

Another study using secondary data from the National Hospitalization Information System analyzed hospitalizations for all-cause pneumonia (after subtracting hospitalization rates for non-respiratory causes) among 2–24 months-old between January 2005 and August 2011 in five Brazilian cities [22]. Adjusted hospitalization rates for pneumonia decreased significantly between the pre-PHiD-CV period and one year after PHiD-CV introduction in Belo Horizonte (28.7%), Curitiba (23.3%), and Recife (27.4%), where PHiD-CV coverage was approximately 100% in 2011, but not in São Paulo and in Porto Alegre, two cities with lower coverage (~80%) [22]. A study evaluating the impact of PHiD-CV introduction in the city of Guaranésia using hospitalization records and outpatient visits for respiratory diseases showed that the prevalence of community-acquired pneumonia cases in <2 years-old decreased by 40% ($p < 0.05$) after vaccine introduction (2009–2010 vs 2011–2012) [26].

Preliminary results of a population-based study conducted in Goiania between December 2010 and March 2011 using a random sample of 1291 children 7–18 months-old suggest that PHiD-CV VE was 40% (95% CI, 1.4–63%) against community-acquired pneumonia in completely vaccinated children [40]. Another study in Goiania using primary data from an active population-based pneumonia surveillance showed that, from May 2007–2009 to October 2011–2013, all-cause pneumonia admission rates decreased by 13.1% in 2–23 months-old and by 7.4% in 24–35 months-old ($p = 0.06$) [29]. Similarly, in an interrupted time-series analysis of data from the Brazilian Hospitalization System from 2005 to 2013 (excluding 2010 and the 2009 H1N1 influenza pandemic months), pneumonia hospitalization rates in 2–23 months-old decreased by 16.6% after PHiD-CV introduction [41].

Initial results of an interrupted time-series analysis (2005–2012 excluding the 2009 H1N1 influenza pandemic months), using data from the Brazilian Mortality Information System database from all 26 state capitals and the Federal District, showed an overall reduction of 16.9% in pneumonia mortality in 2–23 months-old after PHiD-CV introduction compared to mortality due to other respiratory causes ($p = 0.001$) [42].

Table 2
Impact of PHiD-CV on nasopharyngeal carriage and herd protection in Brazil.

Reference	Region/city	Study type	Study period	Sample size	Age group	Outcome	Effectiveness or percent decrease (95% CI)	Incidence or percentage of cases	
								Pre-introduction	Post-introduction
Andrade et al. [17]	City of Goiania	Cross-sectional population-based household survey	December 2010–February 2011	1287 children	7–18 months	VT carriage (3 doses) VT carriage (2 doses) 1 catch-up dose	44.0% (14.0–63.5%)[a]; $p = 0.008$ 35.9% (4.2–57.1%)[a]; $p = 0.03$ No effect[a]; $p = 0.905$	–	–
Andrade et al. [40] (abstract)	City of Goiania	Population-based study	December 2010–March 2011	1291 samples	7–18 months	All-type carriage (complete vaccination) All-type carriage (incomplete vaccination)	36% (12–53%)[a] 26% (0–50%)[a]	–	–
dos Santos et al. [21]	City of São Paulo	Time-series analysis (University hospital)	Pre: January 2006–June 2010 Post: July 2010–September 2012	259 patients (170 in ≥2 years)	≥2 years	VT IPD Overall IPD	2–14 years: 65.4%[b]; NS ≥15 years: −32.9%[c]; NS 2–14 years: 24.8%[b]; NS ≥15 years: −83.7%[c]; NS	$2.81/10^3$ $0.85/10^3$ $3.35/10^3$ $1.72/10^3$	$0.97/10^3$ $1.13/10^3$ $2.52/10^3$ $3.16/10^3$
Caierão et al. [23]	City of Porto Alegre	Retrospective study	Pre: 2007–2010 Post: 2011–2012	325 isolates overall	All ages (mean, 45.2 years)	VT IPD	No decrease[b]; $p = 0.5411$	51.5%	48.1%
Brandileone et al. [33] (abstract)	Nationwide	Passive surveillance	Pre: 2008–2009 Post: 2011–2012	2399 isolates overall	≥2 years	VT IPD (annual median of isolate numbers)	2–4 years: 50%[b]; $p = 0.048$ 5–49 years: 40%[b]; $p = 0.005$ 50–64 years: 47%[b]; $p = 0.021$ ≥65 years: NS[b]; $p = 0.662$	–	–
Andrade et al. [28]	Nationwide	Interrupted time-series analysis (IPD data from SINAN and PM cased from IAL)	Pre: 2008–2009 Post: 2011–2013	9827 cases overall	≥2 years	Overall IPD	2–4 years: −14.7% (−115.1 to 85.7)[c]; $p = 0.347$ 5–9 years: 4.7% (−56.7 to 66.0)[b]; $p = 0.660$ 10–17 years: −6.2% (−85.2 to 72.9)[c]; $p = 0.465$ 18–39 years: −18.9% (−36.7 to −1.1)[c]; $p = 0.018$ 40–64 years: −52.5% (−80.3 to −24.8)[c]; $p < 0.0001$ ≥65 years: −79.3% (−96.5 to −62.1)[c]; $p < 0.0001$	–	–

Azevedo et al. [39] (abstract)	City of Salvador	Prospective laboratory surveillance	Pre: 2008–2009 Post: 2010–2013	–	≥50 years	Overall IPD	≥50 years: 20%[b] ≥60 years: 23%[b]	–	–
Jarovsky et al. [37,38] (abstracts)	São Paulo	Hospital-based retrospective surveillance	Pre: 2007–2009 Transition: 2010 Post: 2011–2014	94 episodes	<16 years	Overall IPD	–	$4.7/10^3$ (transition: $3.7/10^3$)	$2.2/10^3$; ($p = 0.001$)
						VT IPD		62%	35.5% ($p = 0.001$)
						IPD mortality		0.04%	0.07%
Lobo et al. [36] (abstract)	City of Salvador	Hospital-based surveillance	Pre: January 2008–May 2010 Post: June 2010–December 2012	104 cases	All ages	PM	–	$0.71/10^5$	$0.46/10^5$ ($p < 0.03$)
						VT PM		$0.31/10^5$	$0.15/10^5$ ($p < 0.03$)
						PM case fatality rate		24%	17.6%
dos Santos et al. [27]	City of Salvador	Active hospital-based surveillance	Pre: 1996 Post: 2012		All ages	PM	–	$1.65/10^5$	$0.2/10^5$
Andrade et al. [41] (abstract)	Nationwide	Interrupted time-series analysis (Brazilian hospitalization data)	Pre: 2005–2009 Post: 2011–2013	–	≥2 years	Pneumonia hospitalizations	2–4 years: 14.4%[b]; $p = 0.024$ 5–9 years: 17.4%[b]; $p = 0.001$ 10–17 years: 14.1%[b]; $p < 0.0001$ 18–39 years: 15.2%[b]; $p < 0.0001$ 40–64 years: 4.8%[b]; $p = 0.141$[b] ≥65 years: −9.9%[c]; $p = 0.004$	–	–

CI, confidence interval; IAL, Instituto Adolfo Lutz; IPD, invasive pneumococcal disease; PM, pneumococcal meningitis; NS, statistically non-significant; SINAN, Notifiable Diseases Information System; VT, vaccine-type (serotypes 1, 4, 5, 6B, 7F, 9V, 18C, 19F, and 23F).

[a] Effectiveness.

[b] Percent decrease.

[c] A negative value indicates an increase.

Table 3
Impact of PHiD-CV on pneumonia, acute otitis media, and sinusitis in Brazil.

Reference	Region/city	Study type	Study period	Sample size	Age group	Outcome	Percent decrease (95% CI)	Incidence	
								Pre-introduction	Post-introduction
Scotta et al. [20]	Nationwide	Retrospective analysis (data from DATASUS)	Pre: 2002–2009 Post: 2011–2012	15,147,996 admissions, including 3,514,750 for pneumonia (23.2%)	<4 years	Pneumonia hospitalizations	12.7%; $p < 0.001$	$2801/10^5$	$2447/10^5$
Afonso et al. [22]	5 state capitals	Interrupted time-series analysis (individual-level secondary data)	Pre: January 2005–February 2010 (except Porto Alegre: May 2010) Post: 4 months after introduction–August 2011	197,975 hospitalizations, including 59,636 for pneumonia (30.1%)	<2 years	Pneumonia hospitalizations (adjusted for non-respiratory causes hospitalizations)	Belo Horizonte: 28.7%; $p = 0.002$ Recife: 27.4%; $p = 0.007$ Curitiba: 23.3%; $p = 0.011$ Porto Alegre: 2.3%; $p = 0.845$ São Paulo: 1.8%; $p = 0.827$	–	–
Abrão et al. [26]	City of Guaranésia	Cross-sectional study in primary care and hospitals	Pre: 2009–2010 Post: 2011–2012	377 records	<2 years	CAP AOM Sinusitis	PR: 0.60 (0.46–0.78); $p < 0.05$ PR: 0.77 (0.60–1.0); $p > 0.05$ PR: 1.05 (0.65–1.70); $p > 0.05$	–	–
Andrade et al. [41] (abstract)	Nationwide	Interrupted time-series analysis (Brazilian hospitalization data)	Pre: 2005–2009 Post: 2011–2013	–	<2 years	Pneumonia hospitalizations	16.6%; $p = 0.016$	–	–
Andrade et al. [40] (abstract)	City of Goiania	Population-based study	December 2010–March 2011	1291 samples	7–18 months	CAP (complete vaccination)	40% (1.4–63%)		
Sgambatti et al. [29]	City of Goiania	Active population-based surveillance	Pre: May 2007–April 2009 Post: November 2011–October 2013	8191 samples	2–23 months 24–35 months	All-cause pneumonia hospitalizations	2–23 months: 13.1% (12.9–13.4) 2–11 months: 12.6% (12.3–12.9) 12–23 months:14.2% (13.7–14.6) 24–35 months: 7.4% (7.1–7.8)	$5728/10^5$ $6788/10^5$ $4802/10^5$ $2408/10^5$	$4976/10^5$ $5935/10^5$ $4122/10^5$ $2229/10^5$
Minamisava et al. [42] (abstract)	26 state capitals and Federal District	Interrupted time-series analysis (Brazilian mortality data)	Pre: 2005–2009 Post: 2011–2012	–	<2 years	Pneumonia mortality	16.9%; $p = 0.001$	–	–
Sartori et al. [43] (abstract)	City of Goiania	Time-series analysis (individual-level secondary data)	Pre: January 2008–May 2010 Post: June 2010–August 2013	456,153 outpatient visits, including 6177 (1.4%) due to all-cause otitis, and 241,379 (52.9%) to other causes.	<2 years	Outpatients visits for all-cause AOM	44.5% (43.2–45.7%); $p < 0.0001$[a] 1.58% (0.41–2.73%) monthly; $p = 0.009$	–	–

AOM, acute otitis media; CAP, community-acquired pneumonia; CI, confidence interval; PR, prevalence ratio.

[a] Personal communication.

3.4.2. In the unvaccinated cohort

Preliminary results of a study using data from the Brazilian Hospitalization System from 2005–2013 (previously described for the vaccinated cohort) showed that, 3 years after PHiD-CV was introduced, hospitalizations for pneumonia were also lower in unvaccinated children and adults <40 years-old (14.1–17.4% decreases), consistent with a herd effect (Fig. 2B, Table 2) [41]. In contrast, pneumonia rates increased by 9.9% in ≥65 years-old. The authors estimated that, nationally, 224,542 hospitalizations for pneumonia were avoided since the introduction of PHiD-CV [41].

3.5. Acute otitis media and sinusitis

One article evaluated the impact of PHiD-CV introduction on AOM and sinusitis (Fig. 2C, Table 3) [26]. This retrospective study found no decrease in the prevalence of all-cause AOM and sinusitis after vaccine introduction (2009–2010 vs 2011–2012) in <2 years-old in the city of Guaranésia. However, in a separate comparison of vaccinated vs non-vaccinated individuals, they mentioned that vaccination protected against AOM (prevalence ratio = 0.47, 95% CI, 0.35–0.64; $p < 0.05$) [26].

Another study in Goiania, presented as an abstract, showed a significant reduction in outpatient visit rates due to all-cause otitis in children 2–23 months-old, 3 years after PHiD-CV introduction [43]. All 2–23 months-old children with all-cause otitis diagnosis between January 2008 and August 2013 were identified, and outpatient visits due to other causes were used as comparators. The rate of all-cause otitis visits per 10,000 children decreased by an average of 1.58% each month (95% CI, 0.41–2.73%; $p = 0.009$) after PHiD-CV was introduced, whereas the rate of visits due to other causes increased by 0.51% (95% CI, 0.06–0.95%; $p = 0.026$) [43]. The overall decrease in all-cause otitis visit rate was 44.5% in the post-introduction period, whereas childcare visits increased by 17.8% (personal communication).

3.6. Nasopharyngeal carriage

One study evaluated the impact of PHiD-CV on pneumococcal nasopharyngeal carriage, necessary for herd protection. This cross-sectional population-based household survey was conducted for 7–18 months-old in Goiania from December 2010 to February 2011 (Fig. 2B, Table 2) [17]. After adjustment for confounding factors, VT carriage rates were lower in children who received two doses (VE, 35.9%; 95% CI, 4.2–57.1%) or three doses (VE, 44.0%; 95% CI, 14.2–63.5%) than in non-vaccinated children. VT carriage was not significantly lower in children who received one catch-up dose between 12 and 23 months of age [17]. A preliminary analysis of this study also suggested that adjusted VE against overall pneumococcal carriage was 36% (95% CI, 12–53%) for complete primary vaccination and 26% (95% CI, 0–50%) for incomplete vaccination [40].

4. Discussion

This review represents the first analysis of the overall impact of a second-generation pneumococcal conjugate vaccine (PCV) on all the major pneumococcal disease manifestations in a single developing country. In children <5 years-old, despite an increased surveillance as of the introduction of PCV in the national immunization program, all studies but one showed a positive impact of PHiD-CV on the incidence of vaccine-type and any-type IPD, including decreases in pneumococcal meningitis morbidity and mortality. Pneumonia hospitalizations and mortality and outpatient visits due to all-cause otitis media also decreased. Nasopharyngeal carriage of VT and any-type pneumococci decreased after the primary doses, with no early signs of replacement with other pathogens. Finally, herd protection against VT IPD and pneumonia in unvaccinated subjects was shown in some studies for some age groups. These findings support cost-effectiveness analysis suggesting that the introduction of PHiD-CV in the national immunization program has the potential to markedly reduce the overall health and economic burden of pneumococcal disease in Brazil [44].

These results are aligned with those from two double-blind RCTs of PHiD-CV in Finland (FinIP; NCT00861380) and Latin America (COMPAS; NCT00466947). Both studies showed that PHiD-CV is highly effective in preventing pneumococcal diseases [45,46]. Similar impact on VT IPD in unvaccinated populations was observed in Brazil and in Finland (Fig. S1). With sustainable and consistent surveillance allied with comprehensive coverage estimations, we believe that Brazil may help provide further information on the duration of protection in the PHiD-CV-vaccinated cohort and the overall impact on IPD in a developing country, including vaccine-related, NVT disease (replacement phenomena), and herd protection.

Overall PHiD-CV coverage rapidly increased after it was introduced; however, vaccination coverage was only 54.6% (95% CI, 52.1–57.7%) in Goiania 6–8 months after its introduction [47]. The national vaccination coverage register reports coverage of ~94% for the 3 primary doses in 2013 and 2014 but information about the booster dose, which is important for the duration of protection, is not found in the register nor in published references [48,49].

Although serotype 19A was not common in Latin America before the introduction of PCVs, the case–control and the indirect cohort studies in Brazil provides reassurance on the effectiveness of PHiD-CV in prevention of IPD due to this serotype [18,19,50,51]. However, the impact of PCVs on overall IPD should be monitored, because it includes VT and vaccine-related-types but also accounts for the emergence of NVT disease.

5. Limitations

A non-systematic review has several limitations such as subjectivity on study selection and lack of analysis of study quality or risk of bias. While we recognize the varying robustness of research methodology across the studies, we did not systematically assess their quality. For instance, some of the studies included were limited by small sample size, unclear population denominators, or risks of bias. Some studies only showed changes in VT IPD and others only on overall IPD. This and the limited age groups examined within a given study can make it difficult to get a complete picture or to determine what might be specifically attributable to vaccination. Also, the age ranges of populations analyzed were not consistent between studies, which may prevent direct comparisons.

Although the surveillance systems were usually based on passive surveillance in hospital settings rather than on more accurate active surveillance, they have produced serotype distribution baseline data that, together with the case control and time-series population analysis, allowed for an initial evaluation of vaccine impact. Use of secondary data such as hospitalization databases may bias the results, for instance due to misclassification or changes in coding practices [52]. A conservative approach using internal controls (e.g., comparison with an unrelated disease rate) was used in some studies to limit biases [17,22,28]. However, this approach may prevent comparisons between studies and may offset a net impact on disease [28].

Pre-/post-introduction analyses should be interpreted with caution because other changes may occur simultaneously to the introduction of the vaccine and skew the results. For instance, the use of PCR for meningitis diagnosis and the shipment of isolates to the central national laboratory both increased after PHiD-CV introduction due to an ongoing case–control study involving

active solicitation of blood culture isolates [18]. It may have offset PHiD-CV impact on IPD, as potentially observed in some of the studies described [22,23]. Analysis of the CVE data showed a general increase in *S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis* cases in children <2 years-old in the São Paulo state in 2010 (Table S1), suggesting a global improvement in case reporting and detection methods. A general increase has not been observed in the SINAN national register for pneumococcal meningitis in <1 years-old, although the numbers of meningococcemia and pneumococcal meningitis slightly increased in all-age population in 2010. Population-based time-series analyses are more robust because they can adjust for pre-vaccination or secular trends [52]. In addition, we think that the reproducibility of the directionality and magnitude of some key results seen here (i.e., decrease in VT and overall IPD in children) provide confidence that these changes are linked to vaccine implementation.

Herd protection against VT IPD and pneumonia in unvaccinated age groups was observed but a detailed analysis of the possible herd effect will require a continuous follow-up. Indeed, all studies but one analyzed data up to 2012 or 2013, which is only 2–3 years after the introduction of PHiD-CV and may not be sufficient to reach the new equilibrium [53–55]. Indeed, experience with the 7-valent PCV (*Prevenar*™/*Prevnar*™, Pfizer) indicated that herd effect is not always apparent in all age groups at the same time [55]. The potential signs of replacement by NVT serotypes should be assessed carefully. In addition, further studies should be done to evaluate the effect of PHiD-CV introduction on diseases such as AOM, sinusitis, conjunctivitis, or exacerbations of chronic obstructive pulmonary disease that might be prevented by the NTHi protein D contained in PHiD-CV [56].

Finally, the two other PCVs have been available in Brazil during the study period and, in theory, may have contributed to the observed effect of PHiD-CV. However, the 7- and 13-valent PCVs were available only through the private health system to a small proportion of the population (<8% of children in 2007) [57,58]. Thus, these vaccines should not have affected the results in the different studies presented here.

6. Conclusions

Pneumococcal disease represents an important health and economic burden in Brazil. Our review shows that PHiD-CV introduction in the national immunization program for young children had a positive impact on IPD, pneumonia, AOM, and carriage, with emerging data on benefits for unvaccinated age groups for IPD and pneumonia. These findings extend the results of RCTs to better understand the public health value of this vaccine after it was introduced in a national immunization program. However, active surveillance of pneumococcal infections, notably due to NVT pneumococci, and comprehensive coverage data is needed to continue evaluating the overall epidemiological impact of PHiD-CV in Brazil.

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Conflicts of interest: M.M., B.H., and O.C. declare that they are employees of the GSK group of companies and own stock in the company. W.P.H. declares that he was employed by the GSK group of companies at the time of manuscript development, owns stock in GSK, and shares patents on a 13-valent pneumococcal conjugate vaccine licensed to Pfizer (but receives no royalties as per industry practice). J.H. declares that her company received consulting fees from the GSK group of companies, Sanofi Pasteur, and Pfizer.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.04.006.

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